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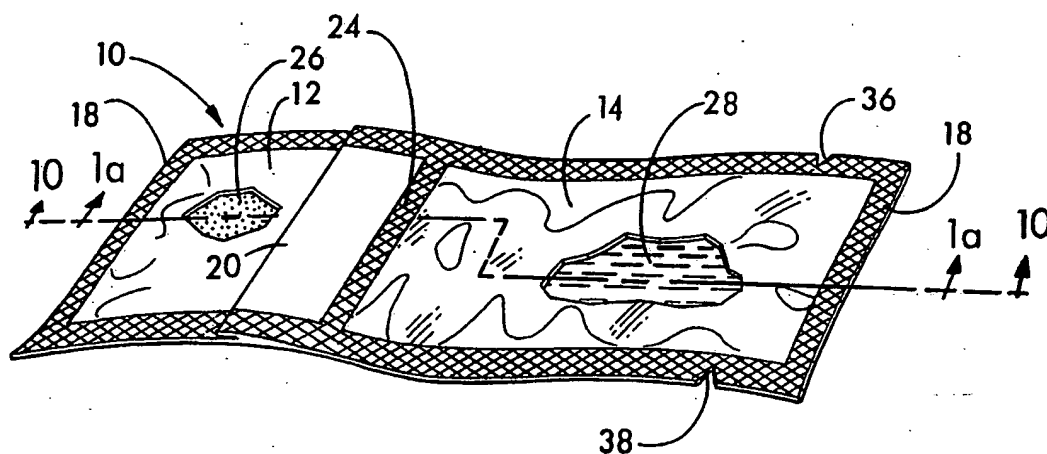
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(54) Title: AQUEOUS GEL WOUND DRESSING AND PACKAGE



(57) Abstract

The invention provides a water-based natural or synthetic hydrocolloidal polymeric gel for dressing wounds or for implantation beneath the skin of a patient that maintains the wound in a moist condition. A gel-forming hydrocolloid polymer in dry particulate form (26), a source of water (28) or an aqueous solution, and optionally drugs and cross-linkers are used in the wound dressing. The liquid and dry solid components are initially separate and are typically contained in separate compartments of a sealed package or pouch (10), but are mixed together within the package after bond (20) is ruptured prior to use. The pouch is formed from flexible sheet material, like paper and plastic (12-16), and sealed at the edges (18). The admixture is sufficiently fluid in consistency to allow it to be poured or spread into the wound. It begins to solidify to form a self-supporting, solid but flexible, dressing structure.

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AQUEOUS GEL WOUND DRESSING AND PACKAGE

BACKGROUND OF THE INVENTION

The healing of wounds, such as wounds resulting from injury, surgical wounds or decubitus ulcers, is greatly dependent upon the dressing used. Conventional bandages often do not provide optimum results. In the case of a decubitus ulcer, treatment should include the removal of necrotic tissue and the establishment of an environment that enhances wound healing. Special pressure-relieving or reducing measures should also be taken. A moist dressing is often beneficial. Some of the advantages of a moist wound dressing are the rehydration of dehydrated tissue; increased angiogenesis, *sis*, i.e., proliferation of new blood vessels; minimized bacterial growth; physical protection; and the maintenance of the proper pH for stimulating the release of oxygen and for allowing proteolytic enzymes to work more efficiently.

In the past, starches in granular form have been applied to wounds and dextrans have been applied as beads or as a paste. Calcium alginates have also been applied to wounds in powdered or granular form. These prior products have certain disadvantages. Powder or granules cannot be applied evenly. Consequently, they do not absorb tissue moisture evenly, causing nonhomogeneous hydration or swelling of the dry granules. Pastes must be spread onto the tissue. Generally speaking, granular absorbent dressings are difficult to remove completely from the wound bed. Dressing changes typically require irrigation of the wound bed to remove the gel granules. The pressure required to spread the paste can be painful or further traumatize the tissue. In addition, an even application is not always easy to achieve because the product retains its plastic

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character. If made part of a cloth bandage, the dressing may not have intimate contact with the tissue. In the case of a powder, sterility may be difficult to maintain because air containing airborne pathogens will enter the package, replacing and contaminating the powdered product as it is poured from the container.

The present invention provides a sterile wound dressing and package which permits the dressing to be prepared from two shelf-stable components and which is initially fluid to facilitate application to the wound but which, after being applied, forms a stable, elastic gel in situ to protect the wound and maintain a moist environment at the tissue surface. The invention also provides a dressing that is shelf stable yet is easily and quickly prepared and applied by health care workers and requires no refrigeration. The new dressing also holds its shape through a wide range of temperatures, i.e., it forms a solid that is temperature non-reversible, and can be removed from the wound bed as a solid plug.

THE FIGURES

Figure 1 is a perspective view illustrating one form of package used in accordance with the invention;

Figure 1A is a semi-diagrammatic cross-sectional view taken on line 1A-1A of Figure 1 showing sterilization of the package;

Figure 2 is a view similar to Figure 1 of an optional, modified form of the package with a clip partially removed;

Figure 3 is a view of the package of Figure 1 on a smaller scale illustrating the mixing of its contents;

Figure 4 is similar to Figure 3 but shows the package being opened;

Figure 5 illustrates the application of the dressing to a wound;

Figure 6 illustrates the dressing after being applied to the wound;

Figure 7 is a vertical cross-sectional view taken on line 7-7 of Figure 6 while the dressing is still fluid;

Figure 8 is a view similar to Figure 7 after the dressing has solidified to form a self-supporting gel;

Figure 9 shows a modified form of package; and

Figure 10 is a greatly magnified diagrammatic vertical cross-sectional view of one form of the invention taken on line 10-10 of Figure 1.

SUMMARY OF THE INVENTION

The invention provides a prepackaged wound dressing comprising a natural or synthetic hydrocolloid in dry particulate form. A source of a measured quantity of water is also provided. Optionally, a biologically active agent is provided. These constituents are mixed just before use to form a briefly pourable, water-based natural or synthetic water soluble or water swellable hydrocolloidal polymeric gel for dressing wounds. Just after mixing, the gel is initially sufficiently fluid to be poured or spread into a wound but after application it soon forms a moist, solid elastic protective body that contains the natural or synthetic polymeric hydrocolloid in a hydrated state. The biologically active agent, when present, is dispersed in the gel. The separate liquid and solid components are preferably contained in separate compartments of the same sealed container for being mixed together just before use. Just after mixing, the liquid component (water) gives the dispersion a fluid consistency initially, allowing it to be poured or spread into or onto the wound and to be precisely applied in the exact quantity and to the precise location required. It is then that the dispersion solidifies to form a solid but elastic and pliable,

-4-

self-supporting moist dressing structure which holds the biologically active agent in contact with the wound.

Water can be provided as one component of the package or, if desired, any available source of water can be used provided it is maintained in a sterile condition when mixed with the dry hydrocolloid. However, to best assure that the entire composition is sterile prior to application and that the correct amount of water is used, it is preferred to provide the required water in either the same container as the solid ingredients or in a companion container which can be easily mixed with the solid constituents under sterile conditions. The dressing becomes molded to the shape of the wound and contains a large quantity of moisture that will maintain the wound in a moist condition.

DETAILED DESCRIPTION OF THE INVENTION

In a preferred form of the invention, both solid and liquid constituents, typically a dry hydrocolloid polymer in particulate form, water and a biologically active agent, are prepackaged in a container having at least two separate compartments. The water is separate from the dry hydrocolloid polymer. The invention facilitates mixing of these constituents under sterile conditions while still enclosed in the same package provided for shipping and storing the product. It is also preferred that a portion of the package be removed to enable the initially fluid gel, which is in a pourable condition, to be easily expelled onto the wound. The hydration of the dry particulate hydrocolloid begins the moment the solid and liquid constituents come in contact with each other, i.e., upon mixing. The product, a dispersion, is, however, liquid at this stage and therefore can be easily applied to cover or fill a wound of any shape. As soon as it is

SUBSTITUTE SHEET

-5-

applied, the dressing occupies the void within a wound. The lower surface of the dressing has the same contour as the wound itself, i.e., the wound serves as a mold for shaping the dressing which then begins to solidify into a solid but flexible, three-dimensional form. The gel thus formed in the wound is also strong enough to allow for easy removal and to provide some cushioning for the wound bed, i.e., protecting the wound. Besides maintaining a moist wound surface, the dressing also absorbs exudate from the wound and supplies the biologically active agent to the tissue.

In a typical application, the freshly mixed solid and liquid components will remain fluid and pourable for about 10 seconds to 3 minutes. When the temperature is elevated above room temperature, the composition tends to solidify more rapidly. For example, at 34°C, one composition of the present invention reaches 6 million centipois in about 25 minutes, whereas at 15°C it takes an hour. Other factors that affect the length of time that the dispersion remains as a fluid and the ultimate strength of the gel include the chemical composition of the polymer and cross-linker, if any, as well as the concentration of each. It is highly preferred that the liquid dispersion have sufficient body or viscosity to allow the wound to be filled with little or no tendency to flow out of or away from the wound; i.e., it is preferred that the dressing is not watery enough to flow or drip from the wound.

The term "gel" herein refers to a solid or semi-solid, elastic, pliable substance formed by the solidification of an aqueous colloidal dispersion. The term "fluid" refers to a water-based hydrocolloidal composition that has sufficient liquidity to be poured or spread onto a wound. The chemical composition of the natural or synthetic hydrocolloidal polymer employed

should be selected to form a gel spontaneously after hydration or, if desired, the hydrocolloid can be one requiring a cross-linking agent to induce or enhance solidification of the polymer. The present invention
5 encompasses both of these systems.

The unique wound dressing of the present invention is easy to ship and mix. It is also easy to apply and use. It is supple, elastic, pliable, soft, semi-solid and conforms naturally to the contours of the wound.
10 The water in the dressing keeps the wound moist. The dressing is non-irritating, has no odor and promotes healing. The dressing will remain in place after application but can be easily removed as a solid plug.

The invention is illustrated by way of example in Figures 1-7 and 10. Shown in Figures 1-7 and 10 is a container 10 or pouch formed from flexible sheet material including upper and lower superimposed sheets, in this case consisting of an upper sheet of a fibrous material, e.g., paper 12, an upper sheet of plastic film 14 and a
20 lower sheet of plastic film 16. The sheets 12-16 are sealed together at their edges, e.g., by means of heat and pressure (a heat seal) to form a permanent peripheral fin seal 18 which extends around the entire container 10. The paper sheet 12 is sealed to the plastic sheet
25 14 along a transverse heat seal line 20.

Extending between upper and lower edges of the pouch 10 is a rupturable seal 24 which includes a rupturable bond 22 (Figure 10) between sheets 14 and 16. Communication inside the container 10 on either side of
30 the rupturable seal 24 is prevented by means of bond 22. In this way, two separate compartments are formed to prevent contact between a dry particulate pharmaceutical constituent 26 on one side of seal 24 and liquid constituents 28 (water) on the other side. The term "water"
35 herein includes aqueous solutions as well as pure water. The package 10 is shipped as shown in Figure 1 with the

water 28 separated by seal 24 from the dry particulate pharmaceutical constituents 26, thereby providing excellent shelf-life for the dry ingredients 26 which at this stage are inactive.

5 The package containing liquid and solid constituents 28, 26 is preferably sterilized. In this case, the contents are sterilized as shown in Figure 1A. The paper sheet 12 is porous but impervious to pathogenic organisms. Its porosity allows a sterilizing agent such
10 as ethylene oxide gas to be introduced into the pouch 10 to the left of the barrier 24, e.g., through a gas applicator manifold 30. Exposure to ethylene oxide for a period of six hours has been found satisfactory. The liquid constituents 28 to the right of the barrier 24
15 are sterilized by being exposed to ionizing radiation 32 from a gamma radiation source 34 of ≥ 2.5 Mrad.

The paper sheet 12 can be 37.5-pound per ream porous, waterproof paper formed from polytetrafluoroethylene, e.g., Tyvek® paper 1073B or 1059B (available
20 from DuPont, Inc. of Wilmington, Delaware), and the plastic sheets 14, 16 can be a 5 mil laminate, e.g. of polyethylene, aluminum foil, polyethylene and Mylar® as available from Technipaq Corporation of Chicago, Illinois.

25 One suitable plastic resinous film (Figure 10) used for the sheets 14 and 16 comprises a five-layer laminate which is formed from the following materials listed from the outside proceeding inwardly: first, a 0.5 mil layer 15a of saran-coated polyester film, e.g.,
30 M-30 which is a product code number of the DuPont Company; next, a polyacrylic adhesive layer 15b to bond the outer film layer to the third layer 15c which comprises a 0.6 mil layer of oriented biaxial nylon; next, an additional polyacrylic adhesive layer 15d; and
35 finally, the innermost layer 15e which comprises a frangible substance that will separate under predeter-

mined conditions. The bond 22 should be composed of a frangible material with a controlled, i.e., reduced peel strength. While various frangible heat-sealing substances can be used that are known to those skilled in the art, one preferred heat-sealing substance is an ionomer comprising a zinc salt of an ethylene acrylic acid copolymer known as Surlyn® by E.I. duPont of Wilmington, Delaware. The entire five-layer laminate 14, 16 is also available from the Hargro Flexible Packaging Company of
10 Exton, Pennsylvania as product code F 92-LT-1.

Thus, it can be seen that the rupturable seal 24 consists of a bond 22 wherein the frangible ionomer layer 15e on the inner surface of the sheets 14 and 16 is bonded to itself. An ionomer coating 15e has been
15 found to be surprisingly effective in forming two kinds of bonds: first, the bond at 18 which is very difficult to break and the second at bond 22 which, although durable and strong, will still rupture reliably when manual pressure is applied to the liquid 28 to the right
20 of the bond 22. Thus bond 22 can be reliably ruptured at ambient temperature solely by the application of external manual pressure applied to the liquid 28 in the compartment at the right in the figures.

The permanent seal 18 that extends around the
25 entire periphery of the package 10 and the seal 24 between sheets 12 and 14 can be formed with a suitable heat sealer by applying heat and pressure; for example, at 430°F for one second at a pressure of 60 to 80 psi. The permanent seal 18 will typically have an average
30 burst strength of about 4188 g/in at room temperature after one week of storage.

The rupturable seal 24 can be formed at a pressure of 60 psi applied for one-half second at 230°F. This will give the rupturable seal 24 a burst strength of
35 about 450 grams/inch at room temperature after one week's storage. As a result, the seal 24 can be broken

by applying manual pressure to the external walls of the fluid-containing compartment at the right of seal 24 at ambient temperature. This will cause the fluid to spurt through the bond 20 into the compartment at the left and become mixed with the dry constituents 26 to form a dispersion which can then immediately be expelled from the package and applied to the skin of a patient. After bond 22 is ruptured, mixing of solid and liquid ingredients can be accomplished manually, if needed, by kneading the pouch as shown in Figure 3, for from a few seconds to about one minute until a homogeneous slurry is produced.

While performance will vary with different flexible sheet material, if the laminate referred to above is used the following performance will result. The fluid-containing compartment will have a moisture vapor transmission rate of about 0.024 grams/100in²/24hr at 73°F and 90% relative humidity. The oxygen permeability of the same compartment is 0.1982 cc/100in²/24hr at 77°F and 100% relative humidity.

As shown in Figure 4, the end portion of the package 10 above the indentations 36, 38 is removable. At this stage the aqueous hydrocolloid dispersion is a liquid and preferably sufficiently fluid to allow it to be poured into the wound as shown in Figure 5. The dry solid constituents 26 begin to hydrate the moment the solid and liquid contact each other. After mixing, the mixture will remain fluid and pourable for typically about 10 seconds to 3 minutes. During this time, while the hydrocolloid dispersion is fluid, it will typically have a viscosity of less than 6,000,000 cp (Brookfield). It should at least be sufficiently fluid to allow it to be easily spread onto the wound, e.g., with a spatula. However, pouring is preferred.

It will be noticed that the liquid hydrocolloid mixture 52, as it is poured from the package 10 into the

wound 41, will form a three-dimensional body substantially filling the wound; in other words, having a lower surface which conforms exactly to the shape of the wound. The hydrocolloid is in effect molded by the contour of the wound. Within a short time after application, typically five to ten minutes, the liquid hydrocolloid 52 solidifies to form a three-dimensional, self-supporting solid but elastic dressing body 54 with a substantially flat or slightly upwardly curved upper surface 56 and a lower surface 58 which conforms to the lower surface of the wound 41.

The combination of gas pervious (12) and gas impervious (14, 16) materials in a single container has highly beneficial and unique properties, allowing a liquid to be held on one side of the barrier 22, 24 and a dry ingredient on the other side but both can be efficiently sterilized while in the same package. In this way, the package 10 provides for two kinds of sterilization in a single package. This is accomplished by providing two distinct components; paper 12 and plastic 14, 16. This eliminates the need for filling the package under sterile conditions which can substantially complicate and increase the cost of assembling packages. Thus, the invention provides the ability to mix two separate sterile components just before use. A sterile dressing can thus be delivered to a wound whenever needed with no requirement for refrigeration.

The invention can be applied to all kinds of wounds, including abrasions which are flat, but it is particularly useful in filling a wound which has a cavity or uneven surface. The unique wound dressing body 54 is easy to apply and use. The dressing 54 is supple, pliable, soft, solid but elastic, and conforms exactly to the contours of the wound 41. The moisture in the dressing 54 facilitates healing. The dressing is non-irritating, has little odor, and promotes healing.

-11-

The dressing 54 will remain in place after being applied to the wound 41, but it can be easily removed later when required. Besides maintaining the wound 41 in a moist condition, the dressing 54 will absorb exudate from the wound as well as evaporate moisture from its top surface.

The solid dressing 54 is also non-cytotoxic. Removal of the dressing as a solid plug which is then weighed provides a convenient method of monitoring progress of wound healing. Since it is elastic, the dressing provides a cushioning function for the wound.

Refer now to Figure 9 which illustrates a package that includes a flexible envelope 64 similar to the envelope 12 sealed along its edges as shown at 66, e.g. by means of a heat seal, and containing the same dry powdered dressing composition 26 as well as a pressure-rupturable envelope 68 containing water in which is dissolved a cross-linking agent when used and sealed along its edges at 70 similar to the envelope 12 but having a rupturable section 72 in which the seal 70 is narrower and hence weaker to provide a sealed vent opening at 72 which will rupture when the envelopes 64 and 68 are pressed between the fingers, thereby expelling the water 28 from envelope 68 into the dry gel-forming hydrocolloid polymer particles 26. Continued manipulation causes the solid and liquid to mix, forming a sterile uniform dispersion which can be expelled onto the wound after the envelope 64 is opened.

The following method is used to form and use the package of Figure 9. A predetermined quantity of water is sealed in pouch 68 and is then sterilized, e.g., by gamma radiation as described above. The pouch 68 and hydrocolloid particles 26 are then sealed in the envelope 64 which is preferably composed at least in part of a material such as Tyvek® which is permeable to a sterilizing gas. The envelope 64 is then exposed to a steri-

SUBSTITUTE SHEET

-12-

lizing gas, in this case ethylene oxide as described above. The package is then ready for use.

The hydrocolloid polymer particles employed can be any suitable biocompatible natural or synthetic gel forming hydrocolloid which, when mixed with water, will form a solid temperature non-reversible elastic gel, i.e., flexible hydrogel with or without a cross-linking agent to assist in the formation of a nonfluid dressing. Both the hydrocolloid and the cross-linking agent must, of course, be nontoxic. When boric acid is used as a cross-linking agent, it provides a bacteriostatic effect. Moisture evaporates from the dressing 54, thereby minimizing dimensional changes resulting from wound exudate absorption. Evaporation also cools the gel, which provides a soothing effect for the patient. While constituents can be sterilized before packaging, it is preferred to sterilize them after they are in the package as described above to more reliably ensure sterility.

If the gel forming hydrocolloid polymer is a natural polysaccharide gum, it is preferred that the molecular weight be typically between about 50,000 and 500,000. One preferred natural gum is guar gum in an amount between about 3% and 15% and preferably between 9% and 12%, the balance being water and trace quantities of cross-linker. Another suitable polymer is locust bean gum. Both guar and locust bean gum are polygalactomannan gums. While the quantities of the several components used in the gel composition can be varied widely depending upon the properties employed, at least a sufficient amount of polymer should be provided to give the gel a solid consistency after being allowed to set in contact with the wound. Generally greater amounts of polymer and cross-linking agent provide a more solid dressing. Sufficient water should be present to provide the initial fluidity required for pouring or spreading

the composition onto the wound. When a cross-linker is employed, only enough is needed to cause the polymer to solidify. For most applications, the cross-linking agent can be varied from about 0% to 8% by weight and preferably from about 0.1% to about 5.0% by weight, with the balance, e.g., about 80% to 95% by weight, being water. All quantities herein are expressed as percent by weight.

Any suitable nontoxic cross-linking agent of a composition can be used to form a chemical bond between the molecules of the polymer to gel the dispersion 52, forming a solid body. Examples of cross-linking agents for locust bean gum, guar or chemically modified guar are galactose, organic titanate or boric acid.

When the hydrocolloid is a polyglucomannan (e.g., Konjak®), borax can be used as a cross-linking agent. When xanthan gum is used, a suitable cross-linker for xanthan gum is mannose. If locust bean gum is used as the principle hydrocolloid, lactose or a suitable oligosaccharide can be used. The cross-linked polymers lose water solubility as well as any ability to soften in response to temperature changes. Consequently, once solidified, the dressing is non-thermoplastic, i.e., it will not return to a liquid state by heating or cooling. When a cross-linking agent is used in the following examples, it is packaged with the water. However, if desired, it can be packaged with the dry ingredients.

If desired, any of the following biologically active substances can be included in the composition: medications and disinfectants as well as wound healing enhancers, e.g., a vitamin preparation, blood coagulants for battlefield applications, antiseptic compounds, antibiotic compounds, or a source of oxygen. Among other biologically active substances are astringents, antibiotics, oxidants, proteolytic enzymes, collagen cross-link inhibitors such as natural or synthetic diamines,

-14-

e.g., cystamine or histadine, putrescine, spermidine, cadaverine, alpha, omega diamino polyethylene or polypropylene oxide (available as Jeffamine® from Texaco Chemical, Houston, Texas) and the like, various growth factors, amino acids, macrophage stimulating factors, narcotic analgesics, anesthetics, and the like.

The moisture containing hydrogel can also be molded into an implantable delivery device having the form of a rod, disc or other selected shape and implanted under the skin through an incision made for that purpose. In this application, the gel is formed from a pharmaceutical grade hydrocolloid, such as a pharmaceutical grade guar gum which has the property of providing a low endotoxin content. One or more of the biologically active agents is incorporated into the liquid gel. In forming an implantable delivery device, the freshly prepared liquid gel is poured into a mold to form the implantable delivery unit containing a biologically active agent. The molded unit, e.g., having a rod form, is then implanted through an incision beneath the skin where it serves as an errodable implanted delivery device for delivering the biologically active composition into the bloodstream of the animal or human patient.

While some of the biologically active agents that are listed in examples 44-69 are stable in a liquid or semi-solid gel matrix, most of the biologically active ingredients exhibit their best stability when stored in dry solid state mixed with the dry hydrocolloid which is in particulate form. This is especially true for enzymatic and proteinaceous molecules such as growth factors, some immunostimulators and proteolytic enzymes. The present wound dressing exhibits a great advantage over ordinary dressings since the dressing of the present invention will permit the storage of relatively unstable biologically active molecules in a solid (freeze dried) state. Freeze drying of biologically

active agents (lyophilization) is a common method of preserving many unstable biologically active molecules. Mixing the dried, e.g., freeze dried biologically active agent with liquid components just prior to use in accordance with the present invention will ensure the longest useful lifetime for the biologically active molecules and the resulting gel will hold the biologically active agent in contact with the tissue.

The invention will be better understood by reference to the following additional examples of some of the typical hydrocolloid compositions that can be employed in accordance with the invention. Quantities given are expressed as percent by weight. All quantities in units/g or mg/g refer to grams of the hydrated gel dressing. In all formulations, liquid and solid particulate components are stored separately from one another and are mixed together just before use at approximately room temperature (23°C). Unless otherwise stated, before use the boric acid, borax or other cross-linking agent is present in solution in the water portion of the formula.

EXAMPLES

1

25	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
	Hydroxy propyl guar*	9.0	Dressing thickened
	Boric acid	4.4	very slowly, about
	Borax	0.6	5 minutes
	Water	86.0	pH = 6.2

30 *Galactasol 418®, a hydroxy propyl guar manufactured by the Aqualon Company of Wilmington, Delaware. The hydroxy propyl group can be linked to either the galactose or mannose base of the guar molecule.

-16-

2

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
5	Hydroxy propyl guar	9.0	Liquid phase lasted less than ten seconds. pH = 6.2
	Boric acid	4.5	
	Borax	0.5	
	Water	86.0	

10

3

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
15	Hydroxy propyl guar	10.0	Crosslinks slowly, somewhat brittle gel. pH = 6.5
	Boric acid	4.2	
	Borax	0.8	
	Water	85.0	

4

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
20	Guar (Supercol®)	10.0	Short liquid phase, weak gel.
	Water	90.0	

5

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
25	Boric acid	3.6	Very short liquid phase, nice gel.
	Borax	0.4	
	Guar (Supercol®)	5.0	
	Water	87.0	

30

6

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
35	Boric acid	1.7	Very short liquid phase, chunky gel.
	Borax	0.3	
	Guar (Supercol®)	8.0	
	Water	90.0	

SUBSTITUTE SHEET

-17-

7

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
5	Cationic guar	9.0	Long liquid phase and a soft gel. pH = 6.0
	Boric acid	4.0	
	Water	87.0	

8

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
10	Cationic guar	10.0	Hardened slightly faster than example #7. pH = 5.4
	Boric acid	5.0	
	Water	85.00	

9

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
15	Hydroxy propyl guar*	11.0	Very slow gel formation from liquid phase.
	Dihydroxy aluminum sodium carbonate (DHSC)	1.0	
	.9% saline (NaCl)	88.0	

10

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
25	Hydroxy propyl guar*	10.0	Nice gel within 10 minutes. pH = 6.7
	Citric acid	.01	
	.9% saline (NaCl)	89.0	

11

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
30	Hydroxy propyl guar*	10.0	Slightly weak gel in 10 minutes. pH = 6.7
	Boric acid	1.0	
	Citric acid	.01	
	.9% saline (NaCl)	89.0	

35 *Galactasol 418®, Aqualon Company of Wilmington,
Delaware.

SUBSTITUTE SHEET

-18-

12

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
5	Hydroxy propyl guar*	10.0	Nice gel in 5 minutes. pH = 5.8
	Boric acid	1.0	
	Citric acid	0.1	
	.9% saline (NaCl)	89.0	
	*Galactasol 418®, Aqualon Company of Wilmington, Delaware.		

10

13

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
15	Hydroxy propyl guar	10.0	Lumpy liquid phase lasted less than 15 seconds. pH = 6.6
	Boric acid	0.5	
	Citric acid	0.05	
	.9% saline (NaCl)	89.5	

14

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
20	Hydroxy propyl guar	10.0	Nice gel in 1 minute.
	Boric acid	3.0	
	.9% saline (NaCl)	87.0	

15

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
25	Hydroxy propyl guar	11.0	Gel more brittle than elastic.
	Boric acid	1.0	
	.9% saline (NaCl)	88.0	

16

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
30	Hydroxy propyl guar	10.0	Liquid phase less than 2 minutes; great gel in 30 minutes. pH = 6.6
	Boric acid	1.0	
	.9% saline (NaCl)	89.0	
35			

-19-

17

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
5	Hydroxy propyl guar	10.0	Pourable liquid
	Boric acid	0.5	after exactly 1
	.9% saline (NaCl)	89.5	minute, weak gel.
			pH = 7.0

18

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
10	Hydroxy propyl guar	5.0	Liquid for 30
	Boric acid	1.0	seconds, good
	Guar (Supercol®)	5.0	gel.
	.9% saline (NaCl)	89.0	pH = 6.1

19

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
15	Hydroxy propyl guar	5.0	Gel formed more
	Boric acid	0.5	slowly than
	Guar (Supercol®)	5.0	example #18.
20	.9% saline (NaCl)	89.5	pH = 6.6

20

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
25	Cationic guar*	5.0	Two-phase liquid,
	Boric acid	1.0	chunky gel pro
	Guar (Supercol®)	5.0	duced rapidly.
	.9% saline (NaCl)	89.0	pH = 6.9

*Enhance®, Aqualon Company of Wilmington, Delaware.

21

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
30	Hydroxy propyl guar	9.0	Pourable in 1
	Boric acid	0.25	minute, strong
35	Galactose	2.0	gel.
	.9% saline (NaCl)	88.75	pH = 6.5

SUBSTITUTE SHEET

-20-

22

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
5	Hydroxy propyl guar	9.0	Mixable liquid
	Boric acid	0.5	1 minute, strong
	Galactose*	2.0	gel.
	.9% saline (NaCl)	88.5	pH = 6.4

10 *Other samples are made in which galactose is replaced by galactose pentasaccharide or mannose tetrasaccharide. Another sample is made with a tetrasaccharide containing both mannose and galactose in equal quantities.

23

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
15	Hydroxy propyl guar	9.0	Gel formed in
	Boric acid	0.25	less than 2 minutes,
	Galactose	3.0	strong gel in
	.9% saline (NaCl)	87.75	5 minutes. pH = 6.7

24

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
20	Cationic guar	9.0	Homogeneous
	Boric acid	1.0	liquid more than
	Galactose	1.0	3 minutes.
	Mannose	2.0	pH = 6.3
	.9% saline (NaCl)	87.0	

25

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
30	Cationic guar	9.0	Pourable liquid
	Boric acid	1.0	in 2 minutes.
	Galactose	3.0	pH = 6.2
	.9% saline (NaCl)	87.0	

-21-

26

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
5	Cationic guar	9.0	Thickened more slowly than example #25. pH = 6.3
	Boric acid	1.0	
	Mannose	3.0	
	.9% saline (NaCl)	87.0	

27

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
10	Hydroxy propyl guar	9.0	Gel slightly weaker, more elastic. pH = 7.1
	Boric acid	0.5	
	Lactose	3.0	
	Water	87.5	

15

28

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
20	Hydroxy propyl guar	9.0	Clear translucent gel, fair strength and resilience. pH = 2.8
	Calcium chloride	3.0	
	Citric acid	0.5	
	Water	87.5	

29

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
25	Hydroxy propyl guar	9.0	White, very tough elastic gel. pH = 7.6
	Magnesium carbonate	2.0	
	Citric acid	0.25	
	Water	88.75	

30

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
30	Hydroxy propyl guar	9.0	Nice gel, fairly weak. pH = 6.4
	Potassium antimony tartrate	2.0	
	Water	89.0	

-22-

31

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
5	Hydroxy propyl guar	9.0	Translucent gel. pH = 7.4
	Tyxor*	2.0	
	Water	89.0	

*An organic titanate, namely, titanium-ammonium lactate chelate, available from E.I. duPont of Wilmington, Delaware.

10

32

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
15	Anionic guar	12.0	Much stronger gel than example #31. pH = 6.1
	Boric acid	0.63	
	Borax	4.37	
	Water	83.0	

33

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
20	Glucomannan (Konjak®)	12.0	Long liquid phase, weak gel. pH = 5.4
	Boric acid	2.0	
	Water	86.0	

34

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
25	Hydroxy propyl guar	12.0	Low cross-linking, slimy gel. pH = 4.1
	Borax	0.5	
	Alum	3.0	
	Water	84.5	

30

35

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
35	Hydroxy propyl guar	12.0	Gel had low cohesive strength. pH = 6.8
	Calcium phosphate	3.0	
	Citric acid	0.1	
	Water	84.9	

-23-

36

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
5	Guar (Supercol®)	8.0	Gel forms rapidly and uniformly in about 10 to 15 seconds. pH = 6.9
	Magnesium acetate	2.0	
	Boric acid	0.25	
	Water	87.7	

37

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
10	Xanthan Gum	10.0	Rapid surface hydration.
	Boric acid	3.0	
	Water	87.0	

38

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
15	Xanthan gum	3.0	Lumps from rapid surface hydration.
	Hydroxy propyl guar	6.0	
	Boric acid	0.25	
	Galactose	2.0	
20	Water	88.75	

39

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
25	Xanthan gum	5.0	Lumps from rapid surface hydration.
	Locust bean gum	5.0	
	Boric acid	3.0	
	Water	87.0	

40

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
30	Potassium alginate	3.1	Stiff, gritty gel.
	Calcium sulfate	3.1	
	Trisodium phosphate	1.6	
	Diatomaceous earth	12.2	
35	Water	80.0	

SUBSTITUTE SHEET

-24-

41

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
5	Sodium alginate	3.55	Stiff gel, not very elastic.
	Calcium sulfate	3.55	
	Sodium pyrophosphate	0.71	
	Fine diatomaceous earth	21.28	
	Water	70.91	

10

42

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
15	Boric acid	3.0	Gel strength moderate to low.
	Borax	5.0	
	Guar (Supercol®)	3.0	
	Water	89.0	

43

	<u>Ingredient</u>	<u>% by Weight</u>	<u>Comments</u>
20	Hydroxy propyl guar	15.0	Gel like example #36 except somewhat greater cohesive strength.
	Calcium sulfate	3.5	
	Citric acid	0.1	
	Water	81.4	

EXAMPLES CONTAINING BIOLOGICALLY ACTIVE SUBSTANCES

- 25 In the following examples, the symbol "D" indicates that the biologically active agent is in the dry constituent and "W" in the water.

44

- 30 A dressing is made as in Example #1 except that an antibiotic comprising 5 mg/g neomycin sulfate is added to the dry constituents to prevent and fight opportunistic infections. This medicament-containing dressing gel can be used for treating pathogenic wounds, stasis ulcers and chronic wounds. D

-25-

45

- 5 A dressing is made as in Example #2 except that an antibiotic comprising 400 Units/g of bacitracin is added to the dry ingredients to prevent and fight opportunistic infections. D

46

A dressing is made as in Example #3 except that 500 units/g of polymyxin B sulfate is included for preventing infections. D

10

47

A dressing is made as in Example #4 except that oxy tetracycline HCl is provided in the amount of 30 mg/g for infections. D

48

- 15 A dressing is made as in Example #5 except that 2.5 mg/g of gramacidin is included as an antibiotic for preventing and fighting infections. D

49

- 20 A wound dressing is prepared as in Example #6 except that a coagulant/astringent comprising alum in the amount of 75 mg/g is included to provide an emergency or battlefield dressing for reducing blood loss. W

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- 25 A wound dressing is prepared as in Example #7 except that witch hazel in the amount of 200 mg/g is used as an astringent to provide an emergency or battlefield dressing for reducing blood loss. W

51

- 30 A wound dressing is prepared as in Example #8 with 2% to 10% in separate samples of povidone iodine is included in the composition as a disinfectant for treating pathogenic wounds, stasis ulcers and chronic wounds. D or W

SUBSTITUTE SHEET

-26-

52

5 A wound dressing is prepared as in Example #9 with ozone included in the amount of 50 mg/g as an oxygen base and a disinfectant for treating pathogenic wounds, stasis ulcers and chronic wounds. D

53

10 A wound dressing composition is prepared as in Example #10 with hydrogen peroxide used in the amount of 50 mg/g as a disinfectant for pathogenic wounds, stasis ulcers and chronic wounds. W

54

15 A wound dressing is prepared as in Example #11 containing a proteolytic enzyme comprising 20 units/g of collagenase to provide enzymatic debridement of pathogenic wounds, stasis ulcers and chronic wounds. D

55

20 A wound dressing is prepared as in Example #12 containing a proteolytic enzyme comprising 10 units/g of streptokinase to provide enzymatic debridement of pathogenic wounds, stasis ulcers and chronic wounds. D

56

A wound dressing is prepared as in Example #13 containing a proteolytic enzyme comprising 10 units/g of streptodornase to provide enzymatic debridement. D

57

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A wound dressing is prepared as in Example #14 including a diamine for reducing collagen cross-linking comprising 5 mg/g of putrescine. W

58

30 A wound dressing is prepared as in Example #15 including a polyamine for reducing collagen cross-linking comprising 10 mg/g of spermidine. W

-27-

59

A wound dressing is prepared as in Example #16 including a diamine for reducing collagen cross-linking comprising 15 mg/g of cadaverine. W

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A wound dressing is prepared as in Example #17 including a growth factor comprising 40 units/g of platelet-derived growth factor to enhance natural healing processes and stimulate growth. D

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61

A wound dressing is prepared as in Example #18 including a growth factor comprising 10 units/g of fibroblast growth factor to stimulate growth. D

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62

A wound dressing is prepared as in Example #19 including a growth factor comprising 10 units/g of epidermal growth factor to stimulate growth. D

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63

A wound dressing is prepared as in Example #20 including a growth factor comprising 10 units/g of transforming growth factor to stimulate growth. D

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64

A wound dressing is prepared as in Example #21 including an immuno stimulator comprising 15 mg/g of L-arginine to stimulate the inflammatory phase of wound healing. D or W

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A wound dressing is prepared as in Example #22 including an immuno stimulator comprising 5 mg/g of nitric oxide to stimulate wound healing. D or W

-28-

66

A wound dressing is prepared as in Example #23 including an immuno stimulator comprising 50 mg/g of quadrol to facilitate wound healing. W

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67

A wound dressing is prepared as in Example #24 including an immunostimulator comprising 50 µg/g of muramyl dipeptide to enhance wound healing. D

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A wound dressing is prepared as in Example #25 including an immunostimulator comprising 10 µg/g of macrophage activating factor to facilitate wound healing. D

69

15

A wound dressing is prepared as in Example #26 with 1 mg/g of hyaluronic acid added to facilitate healing of pathogenic wounds, stasis ulcers and chronic wounds. D or W

70

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A wound dressing is prepared as in Example #36 with 20 mg/g of diamino polyethylene oxide (Jeffamine® EDR-148) for reducing collagen cross-linking. D or W

71

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A wound dressing is prepared as in Example #1 with 5 mg/g morphine sulfate added as an analgesic for treating trauma wounds encountered in emergency or battlefield medicine. D or W

72

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A wound dressing is prepared as in Example #6 with 1 mg/g of fentanyl citrate as an analgesic tranquilizer for treating emergency or battlefield wounds. D or W

-29-

73

A wound dressing is prepared as in Example #2 with 5 mg/g lidocaine hydrochloride as a local anesthetic for painful wounds. D or W

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74

10 A wound dressing is prepared as in Example #7 with 10 mg/g of a 100:1 ratio of procaine hydrochloride and epinephrine as a local anesthetic which is also vasoconstrictive. This will lessen bleeding as well as aid in retention of the anesthetic to the site of need. D or W

15 Many variations of the present invention within the scope of the appended claims will be apparent to those skilled in the art once the principles described herein are understood.

-30-

WHAT IS CLAIMED IS:

1. A method of preparing a wound dressing comprising,
providing a dry water soluble or water
swellable natural or synthetic hydrocolloid polymer
in particulate form sealed within a package in a
dry sterile condition,
maintaining the hydrocolloid in a dry state
within the package,
before use hydrating the hydrocolloid by
admixing water therewith within the sealed package
to provide a fluid dispersion which can be poured
from the package or spread onto a surface while the
dispersion is in a fluid state so that a lower
surface of said fluid dispersion conforms to
the surface to which it is applied, and
allowing the dispersion to solidify after
being applied to provide a solid but flexible
hydrated gel dressing for keeping the wound in a
moist condition, for absorbing exudate from the
wound and for cushioning the wound.
2. The method of Claim 1 wherein the hydrocolloid is
sealed in a compartment of the package, water is
sealed in a companion compartment, a manually
rupturable barrier is provided between said
compartments, said barrier is ruptured and said
water and said hydrocolloid are then mixed
together.
3. The method of Claim 1 wherein the hydrocolloid
polymer comprises at least one of the following:
guar gum or one of its derivatives, galactomannan,
glucomannan, xanthan gum, locust bean gum and
algin.

-31-

4. The method of Claim 1 wherein a cross-linking agent is present to enhance gelling of the hydrocolloid, said cross-linking agent comprises at least one of the following: boric acid, borax, an organic titanate, galactose, mannose, lactose, an oligosaccharide containing a monomer selected from galactose or mannose and a source of water soluble cations of calcium, magnesium or aluminum.
5. A packaged water soluble or water swellable dressing for wounds comprising,
- a package containing a quantity of a dry natural or synthetic hydrocolloid polymer in particulate form,
- a source of water separate from the dry hydrocolloid, said water being available for mixing with the dry hydrocolloid polymer,
- said package having a barrier to keep the hydrocolloid polymer dry,
- the barrier being rupturable for permitting admixing said water with the dry, hydrocolloid polymer contained in the package to thereby form a liquid dispersion of the hydrocolloid that can be poured or spread onto the wound and which thereafter solidifies while in contact with the wound to form a solid pliable gel in contact with the wound to serve as a barrier for the wound, to act as a cushion, to provide moisture for the wound and to absorb exudate from the wound.
6. The wound dressing of Claim 5 wherein the hydrocolloid comprises at least one of the following: guar gum, galactomannan, glucomannan, xanthan gum, locust bean gum, algin and the cogeners thereof.

SUBSTITUTE SHEET

-32-

7. The wound dressing of Claim 5 wherein a cross-linking agent is present to enhance gelling of the hydrocolloid.
- 5 8. The packaged dressing of claim 5 wherein the package is a flexible pouch having a first and a second compartment, the first compartment contains the dry hydrocolloid polymer, and the second compartment contains water, and a rupturable barrier is provided for preventing communication between the compartments which upon being ruptured permits communication between the compartments to allow mixing of the contents within the flexible package.
- 10 9. The method of Claim 1 wherein the polymer is sterilized while within the package by exposing the polymer to a sterilizing agency.
- 15 10. The method of Claim 1 wherein the water and the polymer are both sterilized while within the package, the water being sterilized by exposing the package to a first sterilizing agency and the polymer is sterilized by exposing the package to a second sterilizing agency.
- 20 11. The method of Claim 10 wherein the second sterilizing agency is a gas and the package has a porous portion to permit entry of the gaseous sterilizing agency.
- 25 12. The package of Claim 5 wherein the barrier is a seal having a rupturable section which when ruptured provides communication between the compartments so as to allow mixing of the water in one compartment with the dry hydrocolloid in the other compartment.
- 30

SUBSTITUTE SHEET

-33-

13. The package of Claim 5 wherein the container is a pouch formed from flexible sheet material and the pouch is manipulated by hand to cause the water and the hydrocolloid to mix within the pouch to form a dispersion therein while maintaining the sterility of the dispersion, and the sterile dispersion is dispensed from the pouch as a fluid onto a wound after the pouch is opened.
14. The package of Claim 5 wherein the package contains a medicament.
15. The package of Claim 14 wherein the medicament is at least one of the following: a medication, a disinfectant, a wound healing enhancer, a vitamin, a blood coagulant, an antibiotic, and a source of oxygen.
16. A biomedical composition for application to a human or animal body comprising,
a major amount of water;
a minor amount of a natural or synthetic hydrocolloid gel forming polymer comprising at least one member selected from the group consisting of guar gum, cationic guar, hydroxy propyl guar, anionic guar, galactomannan, glucomannan, and the cogeners thereof;
a minor amount of a cross-linking agent comprising at least one member selected from the group consisting of borax, boric acid, a source of borate ions, an organic titanate, galactose, mannose, lactose, an oligosaccharide containing a monomer selected from galactose or mannose, a source of water soluble cations of calcium, magnesium or aluminum, and the cogeners thereof;

SUBSTITUTE SHEET

-34-

said composition comprising a self-supporting solid elastic body.

17. The dressing of Claim 16 wherein the polymer is present in the amount of about 3% to 15% by weight and the cross-linking agent is present in the amount of from about 0.1% to about 5.0% by weight.
18. The dressing of Claim 16 wherein the polymer comprises guar gum in an amount of from about 8% to 15% by weight and the cross-linking agent comprises boric acid in the amount of from about 0.1% to about 1.0% by weight.
19. The package of Claim 5 wherein the barrier comprises a pressure-rupturable seal of relatively low bond strength between the superimposed walls of said package, said seal extending from one side of the package to the other to divide the package into two separate compartments, and the low bond strength of the seal being suited for being forced open by applying manual pressure at ambient temperature to the exterior of the package by pressing on the liquid-containing portion of the package to increase the hydrostatic pressure in the liquid-containing portion and thereby force the liquid through the rupturable seal into the dry constituents contained in the second compartment.
20. The package of Claim 5 wherein the package includes a pour spout and a portion of the pour spout can be removed to allow the contents of the package to be expelled through the pour spout by applying manual pressure to the walls of the package.
21. The package of Claim 5 wherein the package is a pouch formed from a pair of superimposed sheets of flexible material and the pouch has edges that

SUBSTITUTE SHEET

-35-

are sealed together at their periphery to provide a permanent peripheral seal extending around the package for remaining intact after the barrier is ruptured.

- 5 22. The package of Claim 8 wherein the barrier is a rupturable heat seal formed by pressing walls of the package together at a selected temperature, pressure and time to form a bond between the walls that can be ruptured by manual pressure applied to the package at ambient temperature.
- 10 23. The package of Claim 8 wherein the package has a gas permeable portion comprising a flexible sheet formed from fibers of polytetrafluoroethylene.
- 15 24. The package of Claim 5 wherein the container is formed from a plastic resinous film that is permeable to ionizing radiation whereby water contained in the package can be sterilized by exposing the water to ionizing radiation after the water is placed in the package.
- 20 25. The package of Claim 5 wherein the package is formed from at least two different materials for permitting the introduction of different sterilizing agencies into different portions of the package where said different materials are located.
- 25 26. The package of Claim 5 wherein the flexible plastic film has an ionomer coating on an inside surface thereof and said barrier is a heat seal wherein said ionomer coating is present within said heat seal to define a rupturable bond in said barrier.
- 30 27. The packaged wound dressing of Claim 5 or 16 including a medicament comprising at least one of the following: a coagulant, an astringent comprising alum, witch hazel, neomycin sulfate, bacitracin, polymyxin-B sulfate, oxytetracycline

SUBSTITUTE SHEET

-36-

- hydrochloride, gramacidin, providone iodine, ozone,
hydrogen peroxide, collagenase, streptokinase,
streptodornase, spermadine, putrescine, cadaverine,
cystamine, histadine, polyalkyleneoxide diamine,
5 platelet-derived growth factor, fibroblast growth
factor, epidermal growth factor, transforming
growth factor, L-arginine, nitric oxide, quadrol,
muramyl dipeptide, hyaluronic acid, hyaluronic acid
fragment for promoting the healing of pathogenic
10 wounds, an analgesic, a narcotic selected from
morphine, heroin and fentanyl for the treatment of
pain, lidocaine, procaine and epinephrine.
23. The method of Claim 1 wherein a biologically active
agent is provided and said biologically active
15 agent is admixed with the hydrated hydrocolloid so
as to be contained in the wound dressing.
29. The composition of Claim 16 wherein the self-
supporting solid elastic body contains a
biologically active agent and said body is a formed
body that is molded into an implantable delivery
20 device of a selected shape for being implanted
under the skin of a patient through an incision in
the skin.

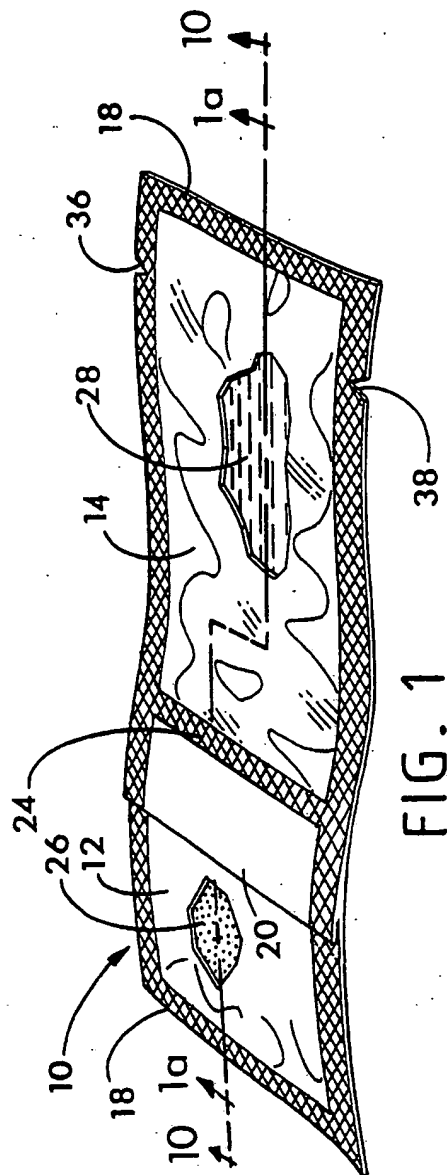


FIG. 1

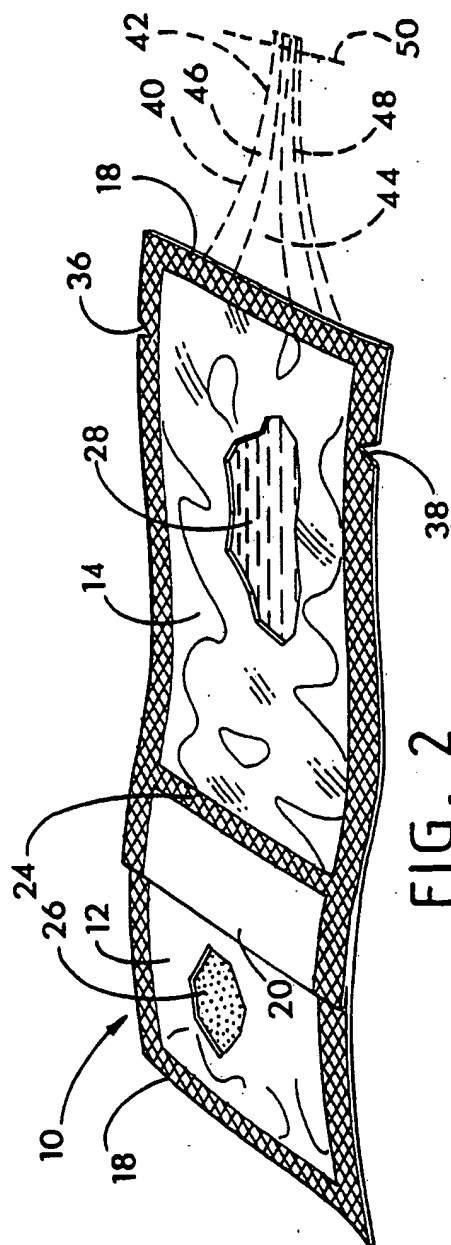


FIG. 2

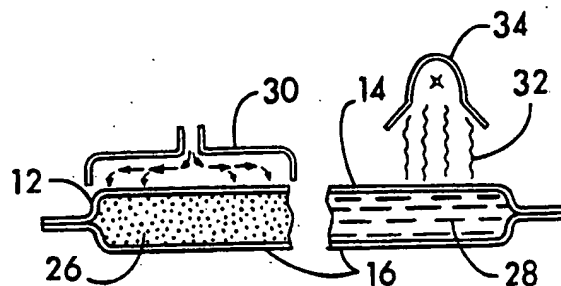


FIG 1a

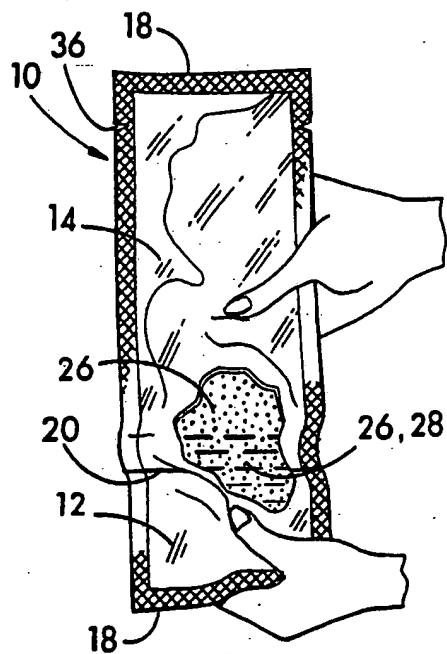


FIG. 3

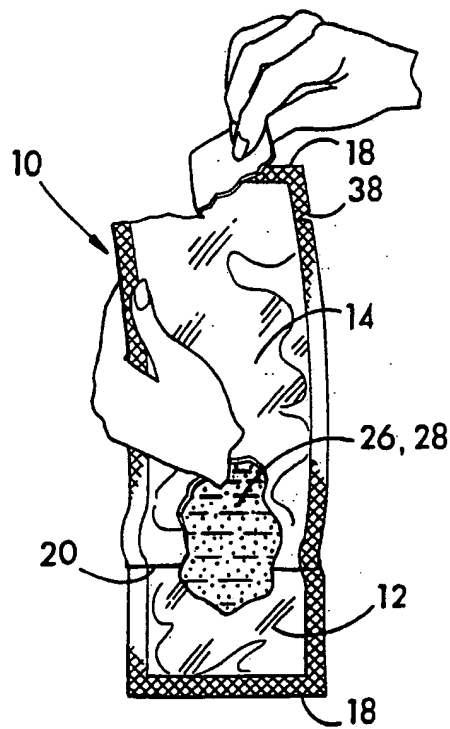
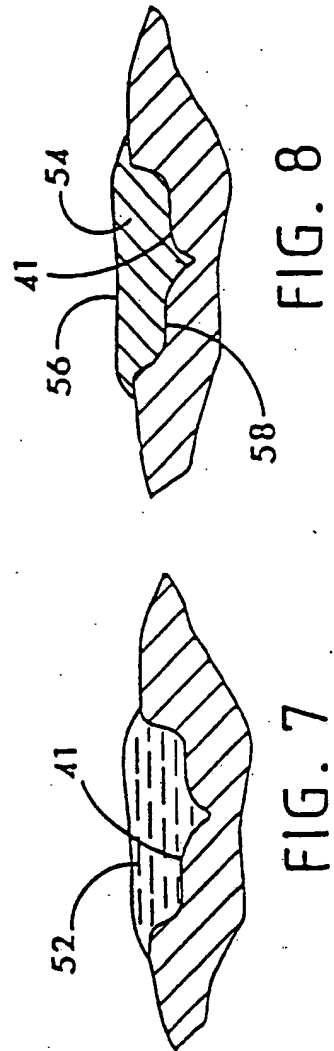


FIG. 4



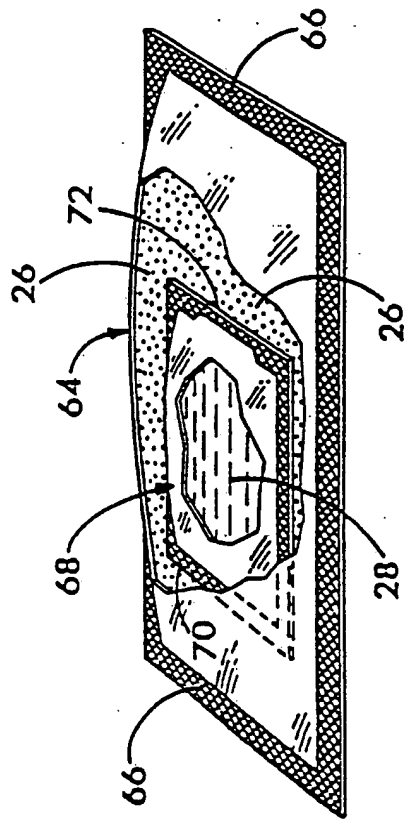


FIG. 9

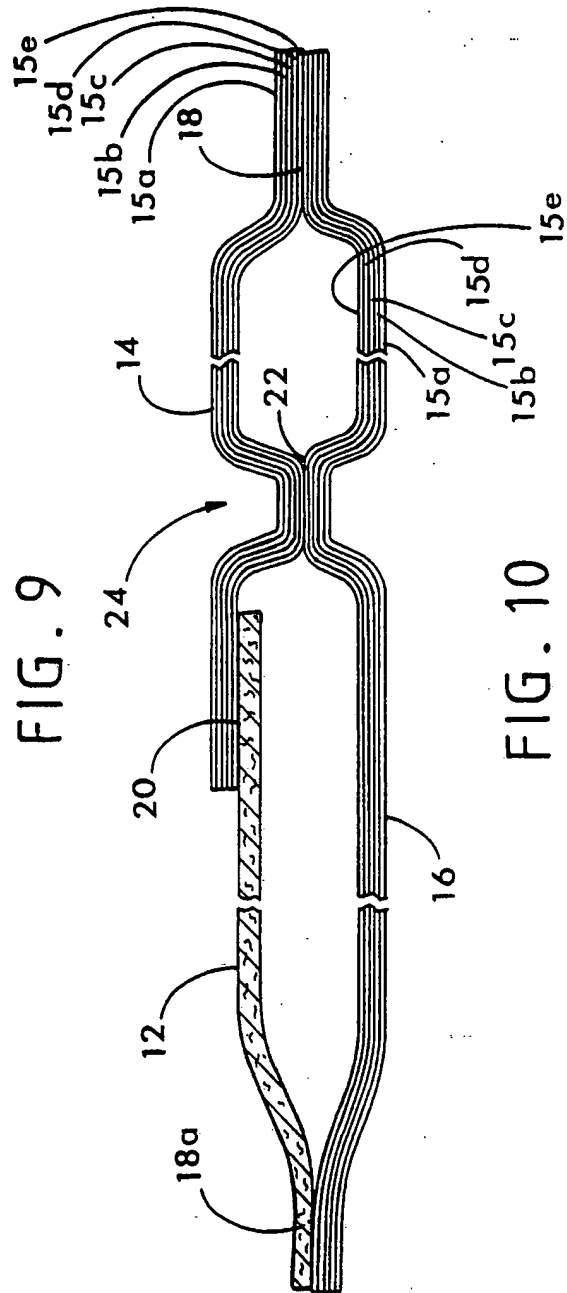


FIG. 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/08403

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61F 13/00

US CL : 424/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/445, 443

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 2,756,874 (ERICKSON ET AL.) 31 JULY 1956; See entire document.	1-29
Y	GB, A, 2,229,443 (AMERICAN CYANAMID COMPANY) 26 SEPTEMBER 1990; See entire document.	1-29

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be part of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"G" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

16 NOVEMBER 1992

Date of mailing of the international search report

31 DEC 1992

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